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Editorial

Giant cell arteritis: Commentary on recommendations of the French Study Group for Large Vessel Vasculitis (GEFA)



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The recently created French Study Group for Large Vessel Vasculitis (GEFA, “*Groupe d’Étude Français des Artérites des gros vaisseaux*”) is a multidisciplinary panel comprised of members committed to the care and study of patients with giant cell arteritis (GCA). While our understanding of the vasculitides has grown, much remains unknown. Treatment is not curative and is associated with significant morbidity [1]. In hoping to inform and guide practitioners, GEFA members have attempted to achieve at least 80% consensus on recommendations for nomenclature, diagnosis and treatment. For each of these topics there exists varying degrees of controversy, making a rigorous examination of available data and provision of sound advice especially welcome. The iterative, consensus-seeking approach taken by GEFA members has been successful and is an important contribution to guiding medical practice. In a field that thankfully continues to evolve, GEFA authors have been cautious to indicate that their judgments and recommendations are provisional and should be updated over time. In that vein, this important paper also provides the reader with a compass to conceive of future work that will enrich the state of the art of large vessel vasculitis (LVV).

In regard to diagnostic recommendations, the authors’ review includes 2 studies that address the utility of clinical features highly suggestive of GCA, and that were also predictive of a positive temporal artery (TA) biopsy. The presence of masseter muscle claudication, diplopia, new onset uncharacteristic/atypical headaches and temporal artery abnormalities on physical examination significantly increased the probability of a positive TA biopsy. Combinations of features such as polymyalgia rheumatic (PMR),

recent onset headaches, masseter muscle claudication and abnormal TA examination findings conferred a positive predictive value of 97% and a positive likelihood ratio of 47 to support a diagnosis of GCA; and disease onset after 70 years of age increased the positive predictive value to 100%. While these associations were only seen in 27% of the patients with PMR, the data would suggest that a TA biopsy (yield for positives being 49–85%) in such patients is likely unnecessary and may even be potentially misleading, encouraging some less experienced practitioners to not treat a patient with convincing clinical evidence of GCA if their biopsy was negative. The cost-effectiveness of a “no-biopsy strategy” in such patients could be assessed with long-term follow up to determine how often such patients with compelling, high probability presentations were later diagnosed with an illness other than GCA.

GEFA provides an excellent review and recommendations for different modes of large vessel imaging. While it is possible to compare the diagnostic performance of imaging of a TA to results of biopsies, pathology–imaging correlations are less feasible for LVV. Pathology–imaging correlation studies with substantial numbers of patients have not been produced for large vessel disease in GCA or other forms of LVV. Consequently, questions about findings such as vessel wall thickening or enhancement being either a reflection of active disease vs damage (e.g. hypertrophy-myointimal proliferation and neovascularization from in-growth of the vasa-vasorum) remain unanswered. Multicenter, prospective studies of patients with possible aortitis and thoracic aortic aneurysms, having PET-CT or MRI/MRA scans prior to aortic reconstruction surgery could answer questions about pathology–imaging correlations.

How often is LVV a component of GCA? The answer to that question is a matter of perspective. If one looks for LVV in GCA by only clinical features, the yield is about 25% [2–4]. However, if one’s screening tool is imaging of consecutive GCA patients, it is much

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higher (77% by CT angiography prior to treatment; similar studies with PET/CT have not been done) [5]. If the frequency of LVV is assessed in consecutive post-mortem patients with GCA it is 100% [6]. These data indicate that LVV is common and mostly subclinical in GCA. Nonetheless, it is important for the following reason. While arguments can be made for the mortality of patients with GCA being no greater than in an age- and gender-matched population, it is clear that mortality is increased in patients in whom GCA has produced a thoracic aortic aneurysm. Such patients have up to a 50% risk of aneurysm rupture, dissection and sudden death. If one accepts this data, then we should all agree that every patient with GCA should be screened for LVV. How then should screening proceed? How cost-effective would it be to evaluate GCA patients with 4 extremity pulse and blood pressure measurements; to listen for bruits over large vessels or at least the thoracic aorta and aortic valve; or obtain an imaging study with low risk of ionizing radiation (e.g. US of aortic valve and root/arch or MRA/MRI in patients with normal renal function)? While we await concrete data to answer these questions, it is clear that the cost of the afore-mentioned clinical assessment is a modest amount of examination time and should be endorsed. Recognizing that the data is incomplete, GEFA recommends “CT or MRI screening for complications of aortitis at diagnosis, then every 2–5 years, provided the patient has no contraindications to a potential aorta repair.” The latter would be the only life-saving intervention in the setting of a dangerously large or rapidly expanding aneurysm. This GEFA recommendation is quite reasonable and also implies repeating aorta and primary branch vessel imaging whenever clinical symptoms or findings reveal new evidence of LVV. US cannot evaluate the entirety of such a large vascular territory. Another point to consider in regard to vessel imaging is the relative value of regional vs entire aorta and branch vessel studies. In our Center for Vasculitis Care and Research, we are often asked to see patients who have been repeatedly evaluated with regional LV imaging. Such anatomically limited studies have the disadvantage of not discovering new asymptomatic lesions which would signal inadequate therapy to achieve disease control. Lesions only become symptomatic when flow is diminished to a critical degree and compensatory flow through collateral vessels becomes physiologically inadequate.

The GEFA assessment of biomarkers in GCA is both accurate and discouraging: ... “there are no known specific biomarkers for the diagnosis of GCA or for determining distinct disease phenotypes or prognosis”. While acute phase reactants are helpful in the assessment of disease activity, they lack specificity which is a serious liability in an elderly population prone to numerous comorbid conditions. A great deal of biomarker research has focused on autoantibodies, cytokines and endothelial cell markers of injury or activation. However, when one looks at the pathology of TAs or LVV, the most striking sites of injury are within the media and particularly within vascular smooth muscle cells (VSMC). It would appear that a more thorough evaluation of circulating proteins from targeted tissue substrate, VSMCs, deserves further study.

Glucocorticoids have led to important reductions in GCA-derived morbidity, especially relating to visual loss. In the absence of randomized controlled studies of glucocorticoid use, clinical trialists have selected initial dosing and tapering schedules by consensus of experts. GEFA recommendations are in line with these, as are the authors’ recommendations for the use of low dose ASA (barring contraindications) to diminish the risk of visual loss and stroke. A more controversial area is what to do for patients who relapse once or repeatedly (50–91% of cases), as glucocorticoid doses are tapered [7–9]. While the use of methotrexate (MTX) is endorsed in such cases, GEFA collaborators recognized that the efficacy of MTX in this setting is at best modest. Indeed, in cited studies there were no significant differences in the frequency of adverse events between groups, including those related to glucocorticoid

use. The 3 studies from which recommendations are based included 161 patients [8–11]. MTX-induced pneumonitis did not occur and pancytopenia was rarely seen. Nonetheless, given an elderly population in whom gradual or more acute reductions in renal function are common over time, potential life-threatening complications of MTX therapy are a serious concern. The ongoing randomized controlled trial of tocilizumab and the recently reported association of Varicella zoster virus with GCA [12] may make these issues moot. At present, I agree with the caution to not embrace tocilizumab (or VZV) therapy for GCA until more complete efficacy and toxicity data are released.

Beyond the scope of this study but worthy of the readers’ consideration is the importance of anticipating and monitoring patients with GCA for known glucocorticoid-induced morbidities such as cataracts, glaucoma, osteoporosis, diabetes, and treatment-induced or exacerbated hypertension and congestive heart failure. These complications, which may occur in over 85% of cases (more than 3.3 times that of the general age-matched population) [1], may also lead to diagnostic confusion with relapses (e.g. impaired vision, constitutional complaints and cardiovascular events).

It is not easy for the general internist and even vasculitis specialists to digest and critically analyze the vast amount of data presented and critiqued by the GEFA investigators. Indeed, their recommendations are those of a large team of multidisciplinary experts who have given us an appreciation for existing controversies, sound advice and a promise to revisit this exercise as new discoveries yield greater clarity in the future.

Disclosure of interest

The author declares that he has no competing interest.

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